30. (previously amended) A method of claim 1, wherein the lysozyme is isolated from a natural source such as eggs.
31. (previously amended) A method of claim 1, wherein the lysozyme is produced by a bioprocess such as fermentation.
32. (previously amended) A method of claim 1, wherein the mammal is a human.
33. (previously amended) A method of claim 1, wherein the pneumonia is due to viruses, bacteria, or fungi, including pneumonias related to HIV-induced immunodeficiency
34. (previously amended) A method of claim 1, wherein the lysozyme is administered with a carrier, such as DMSO, an alcohol, or water
35. (previously amended) A method of claim 1, wherein the effective amount of lysozyme is from about 10 micrograms per kilogram body weight per day to about 1 milligram per kilogram body weight per day.

REMARKS

Claim Rejections Under 35USC § 102

1) The Examiner rejects claims 28, 29, 32-34 under USC 102(b) as being anticipated by Luniakin et al, stating that "Luniakin teaches administering lysozyme to a patient for treating pneumonia." For the reasons presented below, reconsideration of the rejection is respectfully requested.

Luniakin only suggests that giving lysozyme in conjunction with antibiotic therapy results in a slightly better outcome than that associated with antibiotic therapy alone. He uses lysozyme as an adjunct to antibiotic therapy, clearly implying that it is not a substitute for the normally prescribed agents. The role of

lysozyme in this combined therapy is unclear. It may only potentiate the activity of the antibiotics and have no direct effect on the pneumonia iteself. One skilled in the art cannot conclude that lysozyme per se may be used to treat pneumonia.

Please note the following referenced remarks in support of the applicants' arguments:

A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be led in a direction divergent from the path that was taken by the applicant [In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)].

A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984).

The rationale for not using lysozyme as an agent for treating pneumonia is based on a number of earlier studies demonstrating that this protein has only limited antibacterial activity in vitro (e.g. Neu et al. Effect of human lysozyme on gram-positive and gram-negative bacteria. Antimicrob. Agents Chemother. 8:442, 1968). Various strategies have been developed to circumvent this limitation. In particular lysozyme has been combined with various antibiotics to treat pneumonia (e.g. Luniakin et al). Only recently has it been shown that lysozyme may interact in vivo with other endogenous antimicrobial peptides, resulting in a much more potent bacteriocidal activity than previously suspected (see enclosed reference by Akinbi et al which postdates the filing of the provisional application on 04/10/2000). Such an unexpected result further supports the nonobviousness of the applicants' claims.

Please note the following referenced remark:

Evid nce of unexpected results must b weighed against evid nc supporting prima facie obviousness in making a final d t rmination of th obviousn ss of th claimed invention. In re May, 574 F.2d 1082, 197 USPQ 601 (CCPA 1978)

As additional evidence of the nonobviousness of the applicants' claims, we again refer to the enclosed reference by Akinbi et al. In para 1, column 1, p 5760, the authors state:

"Despite numerous studies confirming the antibacterial properties of lysozyme in vitro, ***there are no studies that have directly assessed the role of lysozyme in the killing of lung pathogens in vivo."***

Furthermore (p 5764, column 1, para 3):

"The spectrum of lysozyme antimicrobial activity in vitro appears to be relatively narrow, ***leading some investigators to conclude that exogenous lysozyme would be of little benefit in controlling bacterial infection."***

Please note the following referenced remark:

The totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is evidence of nonobviousness [In re Hedges, 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986)].

2) The Examiner rejects claims 28, 29, 32-34 under USC 102(b) as being anticipated by Weaver et al, stating that "Weaver teaches administering lysozyme to treat cystic fibrosis. Since as noted by Weaver involvement of the lungs leads to pneumonia it would be inherent that when one treats cystic fibrosis

one will also treat pneumonia." For the reasons presented below, reconsideration of the rejection is respectfully requested.

Weaver does not teach administering lysozyme to treat cystic fibrosis or pneumonia associated with cystic fibrosis. Weaver teaches the use of a lysozyme fusion protein **as a substitute for lysozyme**, because of the possible toxicity associated with in vivo use of native lysozyme. This clearly differentiates his art from the applicants' claims. One skilled in the art cannot conclude from Weaver et al that lysozyme per se may be used to treat pneumonia.

The nonobviousness of the applicants' claims is also supported in Weaver et al (column 2, lines 18-22), which states:

"While the antibacterial effects of lysozyme in vitro have been well documented, there has heretofore been no way to exploit these effects of lysozyme ***for in vivo use.*** *Previous reports furthermore implied that* ***sustained lysozyme administration would be harmful."***

Claim Rejections Under 35USC § 103

1) The Examiner rejects claims 28-35 under 35 USC 103(a) as being unpatentable over Weaver et al and Gavrilenko et et al, taken with with Kats et al. The rejection is a matter of record. Reconsideration of the rejection is respectfully requested, based on the applicants' arguments of record, which are reprised below.

With regard to the Examiner's reference to Weaver et al as teaching the use of lysozyme to treat pneumonia, it is stated in column 2, lines 18-22, that:

"While the antibacterial effects of lysozyme in vitro have been well documented, there has heretofore been no way to exploit these effects of lysozyme for in vivo use. Previous reports furthermore implied that sustained lysozyme administration would be harmful."

Clearly, Weaver et al are teaching away from the use of lysozyme alone as an agent to treat pneumonia. Indeed, the whole point of the invention described in Weaver et al is to **circumvent any potentially harmful effects of administering native lysozyme** by fusing it with surfactant protein-B. Therefore, the Examiner cannot state that the use of lysozyme to treat pneumonia is made obvious by this reference.

With regard to Gavrilenko et al, the Examiner states that:

"Further, as noted by Gavrilenko, lysozyme is used to treat chronic bronchitis which also leads to pneumonia."

There is no support in the medical literature for the notion that chronic bronchitis leads to pneumonia. Bronchitis (acute or chronic) and pneumonia are two different diseases with different etiologies. Chronic bronchitis is a component of Chronic Obstructive Lung Disease, which encompasses bronchitis, asthma, and emphysema. It involves the upper airways of the respiratory tract and is commonly due to cigarette smoking or exposure to air pollutants, which induce an inflammatory reaction. The Examiner's argument that "...lysozyme is used to treat chronic bronchitis which also leads to pneumonia" is therefore incorrect.

Furthermore, with regard to the Examiner's continued use of the previously recorded prior art (Weaver et al., Gavrilenko et al., Kats et al, he has not considered the applicants' previous arguments (listed above) against the use of these references as prior art. The Examiner is required to provide a rationale for his continued use of these references over the stated objections of the applicants.

When an applicant submits evidence, whether in the specification as originally filed or in reply to a rejection, the examiner must reconsider the patentability of the claimed invention. The decision on patentability must be made based upon consideration of all the evidence, including the evidence submitted by the examiner and the evidence submitted by the applicant. A decision to make or maintain a rejection in the face of all the evidence must show that it was based on the totality of the evidence [In re Eli Lilly & Co., 902 F.2d 943, 14 USPQ2d 1741 (Fed. Cir. 1990)].

Furthermore,

Evidence traversing rejections must be considered by the examiner whenever present. All entered affidavits, declarations, and other evidence traversing rejections are acknowledged and commented upon by the examiner in the next succeeding action. The extent of the commentary depends on the action taken by the examiner. Where an examiner holds that the evidence is sufficient to overcome the prima facie case, the comments should be consistent with the guidelines for statements of reasons for allowance. Where the evidence is insufficient to overcome the rejection, the examiner must specifically explain why the evidence is insufficient. General statements such as "the declaration lacks technical validity" or "the evidence is not commensurate with the scope of the claims" without an explanation supporting such findings are insufficient (MPEP 716.01).

2) The Examiner states that "the language 'consisting essentially of' is interpreted to mean 'comprising' unless applicant can show that the other ingedients in the references would materially change the fundamental characteristics of applicant's invention"

In the face of growing human resistance to antibiotics, there is an unmet need for the use of alternative compounds to treat pneumonia (see enclosed references by Hancock et al and Yan et al). The novel aspect of the applicants' claims is the use of lysozyme per se as an **alternative** (not an adjunct) to antibiotics for the treatment of pneumonia. Inclusion of additional steps materially changes the characteristics of the applicant's invention. In particular, the use of antibiotics in conjunction with lysozyme as indicated by Luniakin is contrary to the thrust of the applicants' claims. The substitution of a lysozyme fusion protein for native lysozyme as taught by Weaver et al also runs counter to the applicants' teaching.

3) The Examiner rejects claims 28-35 under 35 USC 103(a) as being unpatentable over Weaver et al or Luniakin et al, stating that "Both references each teach that lysozyme is administered to a patient having pneumonia or inherently has pneumonia as taught above in Weaver. To use lysozyme from chicken eggs or produced by fermentation, etc. is simply the choice of the artisan."

The applicants' claims are not rendered obvious by either Weaver et al or Luniakin et al for the reasons presented above. Reconsideration of the rejection is therefore respectfully requested.

In summary, it is respectfully requested that these claims now be placed in condition for allowance. Where appropriate, the applicants request constructive assistance with regard to the wording of the claims in order to place them in such condition.

Sincerely yours,

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